Swiss Summary of the Risk Management Plan (RMP)
for

SHINGRIX
Herpes zoster vaccine
(recombinant, adjuvanted)

RMP Summary:	Version 2, July 2022
EU RMP:	Version 7.0, 19 May 2022

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Shingrix is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Shingrix in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

GlaxoSmithKline AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Shingrix.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *Shingrix*

This is a summary of the risk management plan (RMP) for *Shingrix*. The RMP details important risks of *Shingrix*, how these risks can be minimised, and how more information will be obtained about *Shingrix*'s risks and uncertainties (missing information).

Shingrix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Shingrix* should be used.

This summary of the RMP for *Shingrix* should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of *Shingrix*'s RMP.

I. The medicine and what it is used for

Shingrix is authorised for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in

- adults 50 years of age or older; and
- adults 18 years of age or older at increased risk of HZ (see SmPC for the full indication).

It contains the recombinant VZV gE antigen as active substance and the $AS01_B$ Adjuvant System and it is given by intramuscular injection.

Further information about the evaluation of *Shingrix*'s benefits can be found in *Shingrix*'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

// ema.europa.eu/medicines/human/EPAR/*Shingrix*

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Shingrix*, together with measures to minimise such risks and the proposed studies for learning more about *Shingrix*'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of *Shingrix* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Shingrix* are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Shingrix*. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination) • Guillain-Barré syndrome (GBS) • Virus reactivation in individuals with a history of Herpes Zoster
Missing information	• Long-term efficacy and assessment of the need for additional doses of the vaccine in adults of 18 years of age or above • Long-term immunogenicity in adults as of 18 years of age or above • Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

II.B Summary of important risks

Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	
Evidence for linking the risk to the medicine	pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. pIMDs are considered as a theoretical risk for all vaccines containing Adjuvant Systems (i.e. adjuvant combinations). In addition to genetic factors, environmental triggers (in particular, viruses, bacteria and other infectious pathogens) could play a major role in the development of pIMDs [Wraith, 2003]. This has stimulated the debate as to whether such diseases might also be triggered by vaccines, particularly based on their possible effects on the regulation of the immune system and the potential (yet theoretical) concern that they may induce unwanted immune processes in susceptible individuals. Case reports of autoimmune diseases temporally associated with the administration of vaccines (both adjuvanted and non-adjuvanted) have been described in the scientific literature. Most of these reports refer to vaccines targeting viral illnesses. Proposed mechanisms by which vaccines might induce autoimmune diseases are frequently extrapolated from the known capacity of the infectious agents that the vaccine targets [Tavares Da Silva, 2013].
Risk factors and risk groups	Naturally occurring autoimmune diseases are multi-etiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. No specific trend in terms of groups or risks factors has been identified in *Shingrix*.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: EPI-ZOSTER-030 VS US DB, EPI-ZOSTER-032 VS US DB See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Guillain-Barré syndrome (GBS)	
Evidence for linking the risk to the medicine	A post-marketing observational study (draft manuscript) evaluating the risk of GBS following vaccination with *Shingrix* in adults aged 65 years or older enrolled in the Medicare health insurance in the United States indicated an increased risk of GBS during the 42 days following vaccination estimated as 3.13 excess cases of GBS per million doses administered. Some limitation and confounding variables of the study are presented by the authors. Other time-varying confounders such as potential changes in GBS risk over time due to wild-type VZV reactivation are presented as unknown. Moreover, the increased risk was only detected after the first dose ([RR post dose 1 of 9.30 (95% CI: 3.00-28.84)];[RR post dose 2 of 0.22 (95% CI: 0.04-1.22)]) and has only been investigated in individuals aged 65 years or older. It is worth noting that incidence of GBS increases with age (1.65 per 100,000 py in 40-64 YOA; 3.33 per 100,000 PY in 65-79 YOA and 3.07 per 100,000 PY in more than 80 YOA) [Frenzen, 2007]. GSK has also explored the potential confounding role of preceding HZ episode(s) in the occurrence of GBS post vaccination, a self-controlled case series (SCCS) in two US claims databases (Truven Health Analytics' Marketscan commercial (< 65 years old) and Medicare supplemental (>= 65 years old)) (Haguinet, abstract submitted) suggests a confounding effect of HZ episodes on the potential causal association between *Shingrix* vaccination and the risk of GBS. The possible temporal association between HZ disease and GBS has been reported in the literature (Kang, 2010; Anderson, 2020) The review of additional data (including preclinical data, clinical study data, the scientific literature, spontaneous report data in the GSK safety database and external databases such as EudraVigilance and VAERS), does not indicate that there is an increased occurrence of GBS following vaccination with *Shingrix*. When considering 75% of reporting fraction the observed number of cases was above the expected number of cases in Canada, however the expected was included in the 95%CI of the observed. In Germany, USA and worldwide the observed number of cases were below the expected, for several plausible scenarios of background incidence rates and underreporting, based on background data from a 2007 publication [Frenzen, 2007]. However, several limitations inherent to the available data are noted, e.g., possible underreporting or the quality of the spontaneously reported cases (extent of documentation); clinical trials were not designed to evaluate an association between *Shingrix* vaccination and rare diseases. Because of the substantial limitations of the currently available data and confounding variables, the Company has concluded that the

	strength of evidence of the overall data currently available to the Company are insufficient to determine a causal relationship of GBS with *Shingrix*.
Risk factors and risk groups	In North America and Europe, GBS is more common in adults, and the incidence increases exponentially with age (1.65 per 100,000 py in 40-64 YOA; 3.33 per 100,000 PY in 65-79 YOA and 3.07 per 100,000 PY in more than 80 YOA) [Frenzen, 2007]. Approximately two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a gastrointestinal illness or upper respiratory tract infection. Campylobacter enteritis, influenza, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus (HIV), chikungunya, Zika virus, and Mycoplasma pneumoniae have been implicated to be the trigger. Malignancies and surgical procedures also have been suggested to this increase the risk of GBS [Chen, 2020].
Risk minimisation measures	**Routine risk minimisation measures**: Wording in SmPC section 4.4
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: EPI-ZOSTER-030 VS US DB, EPI-ZOSTER-032 VS US DB See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Virus reactivation in individuals with a history of Herpes Zoster	
Evidence for linking the risk to the medicine	ZOSTER-033 was a phase 3 open-label, uncontrolled, study which evaluated the safety and immunogenicity of *Shingrix* when administered IM on a M0/M2 schedule to 96 subjects with a prior physician-documented history of HZ. The occurrence of HZ was not an endpoint of the study; HZ was to be reported as an AE or SAE as applicable. Six subjects (6.3%), two of whom had reported more than one prior episode of HZ (1 participant with 2 episodes and 1 participant with 3 episodes), reported nine episodes of unconfirmed HZ during the study period of M0 – M14. None of these suspected HZ cases were considered related to vaccination by the investigator. Five of the subjects received anti-viral medication. Clinical details which would inform a robust conclusion regarding these events are lacking. As the study was not designed to formally evaluate HZ recurrence (uncontrolled study with a limited sample size and no HZ confirmatory testing), conclusions regarding this aspect of the study

	have to be considered with caution, in particular since some cases were self-reported. In ZOSTER-056, from the 292 subjects with previous HZ, who had received placebo during the ZOSTER 006/022 pivotal studies and subsequently received HZ/su vaccination in ZOSTER -056, only one subject had a clinically confirmed episode of HZ, the episode occurred between Dose 1 and Dose 2 of study vaccination. In post marketing setting, reported HZ episodes in subjects with a previous history of HZ do not suggest a safety concern
Risk factors and risk groups	Subjects with a history of a previous Herpes Zoster. Only people who had natural infection with wild-type VZV or had varicella vaccination can develop herpes zoster. The reasons why VZV reactivates and causes herpes zoster are not well understood. However, a person's risk for herpes zoster may increase as their VZV-specific cell-mediated immunity declines. This decline in immunity can result from increasing age and/or medical conditions and medications that suppress the immune system. A person's risk for herpes zoster increases sharply after 50 years of age [Kawai, 2014].
Risk minimisation measures	**Routine risk minimisation measures**: Wording in SmPC sections 4.4 and 5.1
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: ZOSTER-062 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: ZOSTER-049 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term immunogenicity in adults 18 years of age and older	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: ZOSTER-049, ZOSTER-073 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Short study name: EPI-ZOSTER-031 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of *Shingrix*.

II.C.2 Other studies in post-authorisation development plan

Study short name	**Purpose of the study**
ZOSTER-049 Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older (Category 3)	To investigate long term efficacy, safety and immunogenicity, as well as to assess reactogenicity, safety and immunogenicity of one or two additional doses
EPI-ZOSTER-030 VS US DB Targeted safety study (TSS to evaluate the safety of *Shingrix* in adults ≥ 50 years of age in the U.S (Category 3)	To evaluate the safety of *Shingrix* in older adults (≥ 50 YOA) in the US.
EPI-ZOSTER-032 VS US DB Targeted safety study (TSS to evaluate the safety of *Shingrix* in adults ≥ 65 years of age in the U.S	To evaluate the safety of *Shingrix* in older adults (≥ 65 YOA) in the US

Study short name	**Purpose of the study**
(Category 3)	
ZOSTER-062 Immunogenicity and safety study of *Shingrix* on a two-dose schedule in adults ≥ 50 years of age with a prior episode of Herpes Zoster (Category 3)	To assess safety, immunogenicity and reactogenicity of *Shingrix* in subjects with a previous history of Herpes Zoster.
EPI-ZOSTER-031 Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complication (Category 3)	To estimate the effectiveness of *Shingrix* in preventing HZ, PHN and HZO in US subjects aged 50 years and above, overall and by age groups. To estimate long-term vaccine effectiveness up to 10 years after vaccination with *Shingrix*.
ZOSTER-073 Long term immunogenicity study and assessment of revaccination with 2 additional doses in adult renal transplant participants from ZOSTER-041	To evaluate long term immunogenicity and safety as well as reactogenicity, safety and immunogenicity of revaccination with two additional doses in adult renal transplant subjects from the study ZOSTER-041.